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Corresponding Author: Dr. Olesya Ajnakina,

Corresponding Author's Institution:

First Author: Olesya Ajnakina

Order of Authors: Olesya Ajnakina; Henriette Thisted Horsdal ; John Lally; James H MacCabe; Robin M Murray ; Christiane Gasse ; Theresa Wimberley

Abstract: Large-scale pharmacoepidemiological research on treatment resistance relies on accurate identification of people with treatment-resistant schizophrenia (TRS) based on data that are retrievable from administrative registers. This is usually approached by operationalising clinical treatment guidelines by using prescription and hospital admission information. We examined the accuracy of an algorithm-based definition of TRS based on clozapine prescription and/or meeting algorithm-based eligibility criteria for clozapine against a gold standard definition using case notes. We additionally validated a definition entirely based on clozapine prescription. 139 schizophrenia patients aged 18-65 years were followed for a mean of 5 years after first presentation to psychiatric services in South-London, UK. The diagnostic accuracy of the algorithm-based measure against the gold standard was measured with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). A total of 45 (32.4%) schizophrenia patients met the criteria for the gold standard definition of TRS; applying the algorithm-based definition to the same cohort led to 44 (31.7%) patients fulfilling criteria for TRS with sensitivity, specificity, PPV and NPV of 62.2%, 83.0%, 63.6% and 82.1%, respectively. The definition based on lifetime clozapine prescription had sensitivity, specificity, PPV and NPV of 40.0%, 94.7%, 78.3% and 76.7%, respectively. Although a perfect definition of TRS cannot be derived from available prescription and hospital registers, these results indicate that researchers can confidently use registries to identify individuals with TRS for research and clinical practices.

Dr Olesya Ajnakina, PhD
Department of Psychosis Studies
Institute of Psychiatry, Psychology
and Neuroscience
16 De Crespigny Park, London,
SE5 8AF
Email: olesya.ajnakina@kcl.ac.uk

20th November 2017

Dear Professor Matcheri Keshavan,

Re: Validation of an algorithm-based definition of treatment resistance in patients with schizophrenia

I would be extremely grateful if you could consider the attached manuscript for submission as an original short communication for Schizophrenia Research. This manuscript contains original work that has not been previously published and has not been submitted for publication elsewhere. I can confirm that all authors have contributed significantly to this manuscript, and that all authors are in agreement with the contents of the manuscript.

Large-scale pharmacoepidemiological research on treatment resistance relies on accurate identification of people with treatment-resistant schizophrenia (TRS) based on data that are retrievable from administrative registers. Some of the authors (J.M., C.G., H.T.H. and T.W.), using register data on prescriptions and psychiatric admissions, developed a definition of insufficient response, which is based on the clinical guidelines and recommendations, using the data available in the Danish prescription and hospital registers. While this definition of TRS has already yielded a wealth of insights into treatment-resistant schizophrenia (Wimberley et al., 2016a; Wimberley et al., 2016b; Wimberley et al., 2017a; Wimberley et al., 2017b; Horsdal et al., 2017), its validity against the gold standard definition as based on the NICE guidelines has not been established yet. In this study using an independent, well-characterised and ethnically diverse sample from South-London (UK) we examined the accuracy of the algorithm-based definition of TRS based on clozapine prescription and/or meeting algorithm-based eligibility criteria for clozapine against the gold standard definition in patients with first episode schizophrenia. We additionally validated a definition entirely based on clozapine prescription.

The results showed that the algorithm-based definition TRS had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 62.2%, 83.0%, 63.6% and 82.1%, respectively. The definition based on lifetime clozapine prescription only had sensitivity, specificity, PPV and NPV of 40.0%, 94.7%, 78.3% and 76.7%, respectively. We concluded that even though a perfect definition of treatment-resistant schizophrenia cannot be derived from available prescription and hospital registers, these results indicate that researchers can confidently use registries to identify individuals with TRS for research and clinical practices.

Many thanks in advance for your consideration.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'O. Ajnakina', with a long horizontal flourish extending to the right.

Dr Olesya Ajnakina
Post-Doctoral Researcher
IoPPN, King's College London, UK

Validation of an algorithm-based definition of treatment resistance in patients with schizophrenia

Olesya Ajnakina ^a, Henriette Thisted Horsdal ^{b,c}, John Lally ^{a, d, e}, James H. MacCabe ^{a,f}, Robin M. Murray ^{a,f}, Christiane Gasse ^{b,c}, Theresa Wimberley ^{b,c}

^a Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

^b National Centre for Register-based Research, Aarhus BSS, Aarhus University, Aarhus, Denmark

^c iPSYCH; the Lundbeck Foundation Initiative for Integrative Psychiatric Research

^d Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland

^e Department of Psychiatry, School of Medicine and Medical Sciences, University College Dublin, St Vincent's University Hospital, Dublin, Ireland

^f National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London

* To whom correspondence should be addressed: Dr Olesya Ajnakina, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AF, UK. Tel: +44 (0)20 7848 0518, fax: +44 (0)20 7848 0287, e-mail: olesya.ajnakina@kcl.ac.uk.

Abstract

Large-scale pharmacoepidemiological research on treatment resistance relies on accurate identification of people with treatment-resistant schizophrenia (TRS) based on data that are retrievable from administrative registers. This is usually approached by operationalising clinical treatment guidelines by using prescription and hospital admission information. We examined the accuracy of an algorithm-based definition of TRS based on clozapine prescription and/or meeting algorithm-based eligibility criteria for clozapine against a gold standard definition using case notes. We additionally validated a definition entirely based on clozapine prescription. 139 schizophrenia patients aged 18-65 years were followed for a mean of 5 years after first presentation to psychiatric services in South-London, UK. The diagnostic accuracy of the algorithm-based measure against the gold standard was measured with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). A total of 45 (32.4%) schizophrenia patients met the criteria for the gold standard definition of TRS; applying the algorithm-based definition to the same cohort led to 44 (31.7%) patients fulfilling criteria for TRS with sensitivity, specificity, PPV and NPV of 62.2%, 83.0%, 63.6% and 82.1%, respectively. The definition based on lifetime clozapine prescription had sensitivity, specificity, PPV and NPV of 40.0%, 94.7%, 78.3% and 76.7%, respectively. Although a perfect definition of TRS cannot be derived from available prescription and hospital registers, these results indicate that researchers can confidently use registries to identify individuals with TRS for research and clinical practices.

Key words Treatment Resistance, Clozapine, Schizophrenia, Validation, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value

1. Introduction

Treatment-resistant schizophrenia (TRS) is a major cause of disability and functional impairment worldwide (Kennedy et al., 2014). Approximately 30% of patients with schizophrenia will develop TRS at some point during their illness course (Elkis and Buckley, 2016; Kane et al., 1988) with all standard treatment guidelines recommending these patients be treated with clozapine (National Collaborating Centre for Mental Health, 2009; National Institute for Health and Clinical Excellence guideline, 2014). The gold standard definition of TRS is generally defined as insufficient response to at least two sequential, different antipsychotic medications of adequate doses taken over an adequate time period (National Institute for Health and Clinical Excellence guideline, 2014); though the definition of insufficient response is open to interpretation (Howes et al., 2016).

When using register-based data, response, or lack thereof, to antipsychotics often has to be inferred from data on service use or changes in prescriptions. This has led researchers to design proxy measures of TRS (Huber et al., 2008). Some of the authors (J.M., C.G., H.T.H. and T.W.), using register data on prescriptions and psychiatric admissions, developed a definition of insufficient response, which is based on the clinical guidelines and recommendations, using the data available in the Danish prescription and hospital registers. While this definition of TRS has already yielded a wealth of insights into treatment-resistant schizophrenia (Wimberley et al., 2016a; Wimberley et al., 2016b; Wimberley et al., 2017a; Wimberley et al., 2017b; Horsdal et al., 2017), its validity against the gold standard definition has not been established.

Therefore, we aimed to validate the algorithm-based definition of TRS (Wimberley et al., 2016b) compared to the gold standard definition of TRS using the longitudinal data from a well-characterised sample of patients with first-episode schizophrenia (FES) collected in South-London and who were assessed after first five years of illness (Ajnakina et al., 2017;

Lally et al., 2016). Another more simple definition of TRS is based exclusively on lifetime clozapine prescription, and has been used in a number of studies (Manuel et al., 2012; Wheeler et al., 2014; Wimberley et al., 2016a,b; Horsdal et al., 2017). We additionally validated this clozapine definition, which we expect would have close to 100% in positive predictive value for detecting TRS patients.

2. Methods

2.1. Sample

Participants were recruited as part of the National Institute of Health Research (NIHR) Biomedical Research Centre (BRC) Genetics and Psychosis (GAP) study conducted in South-London, UK. Further details of the sample are available in Supplementary Material and Di Forti et al., 2014. Among 283 first-episode schizophrenia spectrum psychosis patients (International Classification of Diseases (ICD)-10 diagnoses: F20.0, F25.0, F28.0, F29.0) (WHO, 1992), 166 were FES patients (ICD-10 diagnoses: F20.0) who formed our core analytic sample. Ethical permission was obtained from the South-London and Maudsley Mental Health NHS Foundation Trust (SLaM) and the Institute of Psychiatry Research Ethics Committee. All patients gave informed written consent after reading a detailed information sheet.

2.2. Tracing patients and data at follow-up

The patients with FES were traced five years after first contact with mental health services (**Figure 1**). We successfully traced 139 (83.7%) of the original FES cohort, who had received adequate trials of antipsychotic medications during the follow-up to ascertain their treatment resistant status. Because these data additionally included information on patients with first episode of schizophrenia spectrum disorder, we repeated the analyses on the extended cohort of 240 patients. Information at follow-up was collated from the electronic psychiatric records that are the primary clinical record-keeping system within the SLaM Trust (Stewart et al., 2009) using the WHO Life Chart Schedule (LCS) extended version (Morgan

et al., 2014; Susser et al., 2000). We used this measure at the end of the follow-up period to obtain standardised retrospective assessments of patients' experiences, clinical and social outcomes that were reported by treating clinicians for the entire period of illness. The illness period was operationalised as the period from first contact with mental health services to the date of the last assessment recorded in electronic notes. The LCS measure has been widely used in prospective and retrospective studies (Ajnakina et al., 2017; Schoeler et al., 2017). The details of the approach to data extraction are provided in Supplementary Material and elsewhere (Ajnakina et al., 2017; Lally et al., 2016).

Using the LCS extended version we collected detailed information on in-/out-patient medication history including the number of antipsychotic medications used prior to commencing clozapine, medication initiation/discontinuation dates, antipsychotic dose, and the reasons for changing or discontinuing each antipsychotic medication such as lack of therapeutic effects, intolerance of antipsychotic medications or self-discontinuation of each medication (Lally et al., 2016). We extracted detailed information on reasons for each re-admission throughout the entire follow-up period, and corresponding admission and discharge dates.

2.3.2. Gold standard definition of TRS

Following the National Institute for Health and Clinical Excellence (NICE) guideline (NICE guideline, 2014), patients were defined as having TRS if during the follow-up period they showed little or no symptomatic improvement to at least two consecutive treatments with antipsychotic medications of adequate dose and duration (≥ 6 weeks), as ascertained from the clinical records. A non-response to antipsychotic treatment was defined if 1) patients, having been treated with an antipsychotic medication of adequate dose and for an adequate duration did not show improvements in their clinical presentation as recorded by treating clinicians, and/or 2) the documented reason for switching antipsychotic medication was due to a lack of therapeutic response. An adequate daily dose of antipsychotic medication was

defined according to a daily dose of $\geq 400\text{mg}$ chlorpromazine equivalence (Leucht et al., 2014). We only included as TRS cases those patients who failed to respond and not those who were intolerant of antipsychotic medications or those who self-discontinued antipsychotic medication.

2.3.3. Algorithm-based definition of TRS

The algorithm-based definition of TRS was defined as treatment with clozapine in outpatient services and/or meeting the eligibility criterion for clozapine. The eligibility criterion entailed psychiatric hospital admission due to schizophrenia during antipsychotic treatment (as a proxy for insufficient treatment response) within 18 months after having had two outpatient consecutive periods of different treatments with antipsychotic medication for at ≥ 6 weeks' duration (Wimberley et al., 2016a,b). Additionally, we used outpatient lifetime clozapine prescription to define TRS.

2.4. Analyses

The predictive validity of the algorithm-based definition of TRS in determining treatment-resistant cases was evaluated with sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) (Parikh et al., 2008). All analyses were conducted in RStudio version 3.31 (Integrated Development for R. RStudio, Inc., Boston, MA).

3. Results

3.1. Core analytic cohort

The core analytic sample comprised 139 FES patients with a mean 5-year follow-up ($\text{SD}=2.5$). Of these, 75.9% were male, 31.9% were of white ethnicity, and 46.1% were of black ethnicity. Of all patients, 45 (32.4%) met the gold standard definition of TRS. Applying the algorithm-based definition of TRS to the same cohort, 44 (31.7%) of patients were

defined as TRS during the follow-up period. When applying the clozapine definition the proportion of TRS was 16.5% (N=23/139) (Figure 1).

3.2. Validation of the register-based definition of TRS

Sensitivity of the algorithm-based definition in determining TRS cases was 62.2%; specificity was 83.0%; PPV was moderate (63.6%), and NPV for this definition was high (82.1%) (Table 1). Sensitivity and PPV for the clozapine definition compared to the gold standard were 40.0% and 78.3%, respectively. These results remained largely unchanged when the sample was expanded to schizophrenia spectrum disorders (N=240) (Table 1).

4. Discussion

Our results highlight that an algorithm-based definition of TRS, which includes both clozapine prescription and an eligibility criterion for clozapine, has a 64% chance of correctly identifying TRS cases. Sensitivity of this definition was moderate (62%) and higher than for the clozapine definition of TRS (40%). Because clozapine is under-prescribed in clinical practices (Howes et al., 2012), the clozapine definition inevitably omits some TRS patients leading to the reduced sensitivity. In comparison, the TRS definition that additionally includes the eligibility criterion for clozapine is certainly broader in its scope. Still, a readmission could have been due to other reasons than insufficient treatment response, such as treatment intolerance or non-adherence. Therefore, the sensitivity of this criterion for TRS may be improved by encompassing other functional or symptomatic criteria (Lally et al., 2017; Huber et al., 2008). Nonetheless, large population-based registers, including the Danish registries, tend to lack information on symptoms. Additionally for such registers, data on medications is available from outpatient prescriptions only. Not having access to medication histories during hospitalisation may have contributed to the moderate sensitivity and positive predictive values observed for the algorithm-based definition of TRS; though this is also likely to be due to differences in care between the UK and Denmark. Further, the gold standard was based on clinical records and not individual/personal assessments for determining TRS. Because

we validated two measures including clozapine prescription as a criterion for TRS, the gold standard definition of TRS did not include clozapine prescription and might thus not have identified all with TRS from other information available in the UK data. However, nearly all patients prescribed clozapine are TRS, and in the present study we might thus have underestimated the positive predictive values of the algorithm-based definitions of TRS.

Conclusion

The extended algorithm-based definition indicative of insufficient treatment response to first-line treatment with antipsychotic medications and the clozapine definition should be utilised in combination to increase the probability of correctly classifying all true TRS cases.

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Figure Legends

Figure 1. Flow chart documenting how patients with first episode schizophrenia were traced five years after first contact with mental health services

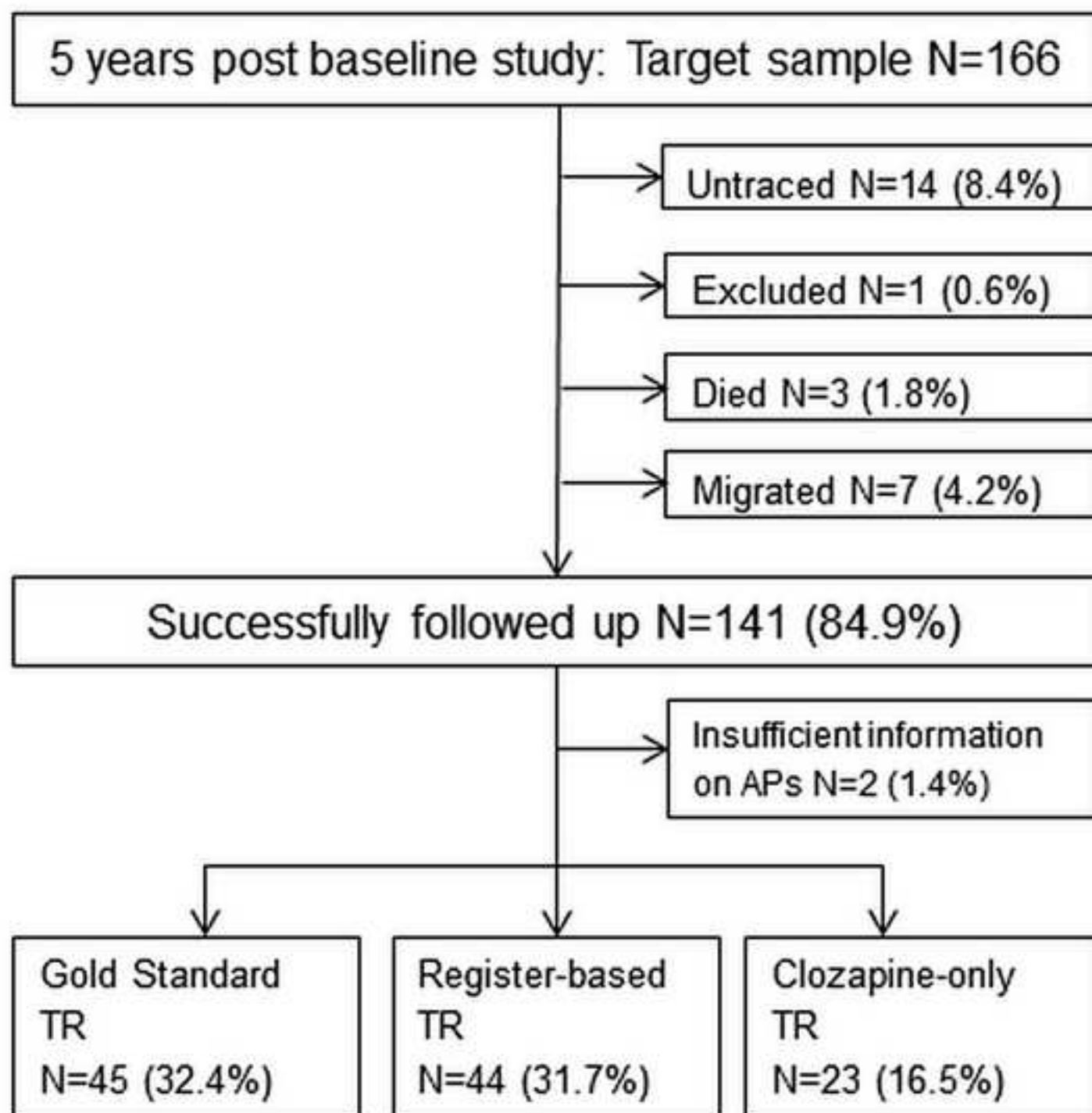
APs, antipsychotic medications

Table 1 Sensitivity, specificity, PPV, and NPV of the two algorithm-based definitions of treatment resistance schizophrenia (TRS) comparative to the gold standard definition of treatment resistance in patients with schizophrenia and schizophrenia spectrum disorders

Definitions of TRS	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Schizophrenia (N=139)				
Algorithm-based TRS (N=44) vs Gold standard (N=45)	62.2	83.0	63.6	82.1
Clozapine (N=23) vs Gold standard (N=45)	40.0	94.7	78.3	76.7
Schizophrenia spectrum disorders (N=240)				
Algorithm-based TRS (N=68) vs Gold standard (N=70)	60.0	84.7	61.7	83.7
Clozapine (N=32) vs Gold standard (N=43)	38.6	97.1	84.4	79.3

TRS, treatment resistant schizophrenia; PPV, positive predictive value; NPV, negative predictive value

Terminology: Algorithm-based - TRS definition combined two criteria for TRS 1) outpatient clozapine prescription; 2) eligible criteria for clozapine; Clozapine definition of TRS is solely based on outpatient clozapine prescription as the criterion for TRS.



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The patients included in the present study were recruited in collaboration with the GAP and PUMP study teams and the South London and Maudsley (SLaM) NHS Foundation Trust. We would like to thank the patients who gave up their time to take part in this study and all of the staff and students who worked tirelessly to collect the data.

Conflict of interests

CG has received grants from LA-SER Analytica and Eli-Lilly, outside the submitted work. JHM has received research funding from Lundbeck. All other authors declare no competing interests. The funders had no involvement in any aspect of the study.

Role of the funding source

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Contributors

CG, TW, JHM and HTH devised the algorithms for detecting TRS in Danish registers. OA was responsible for data management, did statistical analyses, and wrote the first draft of the manuscript. All authors contributed to drafting the manuscript contributed equally to discussion of the study design and results, revised the manuscript, and approved the final version.

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